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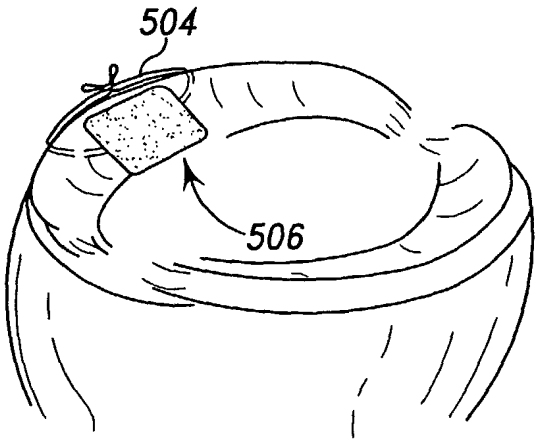
(54) Title: MENISCUS REGENERATION DEVICE AND METHOD



(57) Abstract: Methods and devices are provided for regenerating a meniscus. The devices (20) comprise a layer (22) of toughened naturally occurring extracellular matrix. The devices (20) may, optionally, further comprise a biologic material (60) to provide a framework for meniscus regeneration. The methods comprise the steps of removing a portion of a meniscus to provide a space (16), and inserting a device (20) comprising a layer (22) of toughened naturally occurring extracellular matrix into the space.

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from a material which will withstand the compression and shear stresses involved in articulation of the femur on the tibia, i.e., of the condyles on the tibia platform. It will be appreciated that this is a dynamic stress situation for the upper cover and, for that matter, for the device attached to the surrounding tissue or anchored in the space from which the defected meniscus portion is removed. This upper cover of the device may be provided by treating layers of ECM with heat and pressure to form a toughened upper surface.

In this specification and in the appended claims, unless expressly limited otherwise, it is intended that "toughened" or "treatment for toughening" shall involve treating ECM such as SIS with various treatment steps including such steps as laminating several layers of ECM strips together and treating the layers with compression and vacuum or heat or combinations of pressure, vacuum, and heat. It is contemplated that such layers may be laminated together and bonded by both mechanical compression and application of vacuum and/or heated air which accomplishes the bonding and also dries the product. It has been found that several layers of SIS can be laminated together with heat, vacuum, and pressure to provide a portion of the composite structure. Illustratively, in some embodiments, both the upper cover and the lower cover defining the shell of the device are treated with heat and pressure. It has been found that various drying conditions affect the toughness of the ECM. For example, changing the platen or drying surface in vacuum drying by reducing the size of the openings in the platen can increase the toughness of the resultant ECM. Drying in air or hot air, as compared to in vacuum, can also increase toughness. Any method to increase density, for example by increasing the number of layers of ECM in a given volume, will also increase toughness. Altering the orientation of layers, selecting older animals, selecting species having tougher ECMs, and processing techniques (for example, increasing concentration of peracetic acid or pressure from rollers) can also affect the toughness of the resultant ECM.

Unless otherwise expressly limited, "toughened" or "treatment for toughening" may also include other means of cross-linking ECM. As discussed above, the ECM can be chemically crosslinked to increase the toughness of all or a portion of the ECM through the use of agents such as aldehydes, carbodiimides, glycation agents, enzymes and the like. In addition, as discussed above, other methods of crosslinking the ECM may be used. For example, radiation (including

UV, RF, and gamma radiation) could be used to toughen the ECM. When UV or RF radiation is used, preferably the ECM is crosslinked prior to final drying. Additionally, combinations of methods may be used, such as be drying at elevated temperatures (dehydrothermal crosslinking). All of such methods are intended to be included in the expressions "toughened" and "treatment for toughening" unless expressly limited.

In this specification and claims, unless expressly limited otherwise, "generally wedge-shaped" is intended to define the shape of a device that has a thick base portion and a thin apex portion, wherein the device tapers between the thick base portion and the thin apex portion. Although a generally wedge-shaped device can have flat upper and lower surfaces (see, e.g., Fig. 12), such a device can also have one or more surfaces that are curved, such as a tapering convex surface (see, e.g., Fig. 49) or a tapering concave surface, or could have stepped or contoured surfaces that follow the contour of any underlying material.

In this specification and claims, unless otherwise expressly limited, "mass of biological material' is intended to include naturally occurring extracellular matrix, bioactive agents, and/or biologically derived agents and cells. "Mass of biological material" is also intended to include biological materials formed in whole or in part from such matrices, agents and cells. Thus, "mass of biological material" includes comminuted extracellular matrix and extracellular matrix foams as disclosed in U.S. Patent Application Serial No. XX/XXX,XXX entitled "Porous Extracellular Matrix Scaffold and Method" (Attorney Docket No. 265280-71146, DEP-747), and hybrid materials, as disclosed in U.S. Patent Application Serial No. XX/XXX,XXX entitled "Hybrid Biologic/Synthetic Porous Extracellular Matrix Scaffolds" (Attorney Docket No. 265280-71144, DEP-751), all of which are filed concurrently herewith, and U.S. Patent Application Serial No. 10/172,347 entitled "Hybrid Biologic-Synthetic Bioabsorbable Scaffolds" which was filed on June 14, 2002, the disclosures of which are incorporated by reference herein. Unless otherwise expressly limited, "mass of biological material" includes material from which commercially available products are made, including, for example: the RESTORE® Orthobiologic Implant, available from DePuy Orthopaedics, Inc. of Warsaw, Indiana; OASIS and SURGISIS products available from Cook Biotech, Inc. of Bloomington, Indiana; "TISSUEMEND" available from TEI Biosciences Inc. of Boston, Massachusetts; and

GRAFTPATCH, FORTAFLEX, FORTAGEN and FORTAPERM products available from Organogenesis, Inc. of Canton, Massachusetts. Unless expressly limited otherwise, the expression "mass of biological material" is also intended to encompass purified collagen, such as that disclosed in U.S. Patent No. 6,042,610. The expression "mass of biological material" is intended to encompass all such materials regardless of whether they include another material, regardless of their physical state (e.g., powder or foam), and regardless of whether they are cross-linked or otherwise toughened, unless otherwise expressly stated. The expression "mass of biological material" should be understood to encompass both materials that are integral and that which comprise discrete elements. "Mass of biological material" should also be understood to encompass all forms of these materials, including dry forms, solutions, dispersions, gels, and pastes for example. Specific examples of materials for the mass of biological materials include: comminuted ECM; ECM pieces; ECM foam; an ECM roll; woven ECM; a non-woven ECM mat; braided ECM; ECM solution; ECM dispersion; ECM slurry; ECM gel; ECM paste; and ECM that has not been toughened. Such ECMs include but are not limited to: comminuted SIS; SIS pieces; SIS foam; an SIS roll; woven SIS; non-woven SIS mat; braided SIS; SIS solution; SIS dispersion; SIS slurry; SIS gel; SIS paste; and SIS that has not been toughened.

In the specification and claims, "comminuted" is intended to mean reduced to pieces. "Piece" and "pieces" are intended to mean any fiber, strip, ribbon, sliver, filament, shred, bit, fragment, part, flake, slice, cut, chunk, or other portion of solid or solid-like material. "Comminuted" is not intended to imply any particular means of producing the pieces. No particular shape is intended to be implied by the use of the word "comminuted" unless otherwise expressly limited; the pieces can comprise a variety of two and three dimensional shapes of material. Moreover, unless a specific size of material is specified, the use of the term "comminuted" is not intended to imply any particular size of pieces.

"Bioactive agents" include one or more of the following: chemotactic agents; therapeutic agents (e.g., antibiotics, steroidal and non-steroidal analgesics and anti-inflammatories, anti-rejection agents such as immunosuppressants and anti-cancer drugs); various proteins (e.g., short chain peptides, bone morphogenic proteins, glycoprotein and lipoprotein); cell attachment mediators; biologically active ligands; integrin binding sequence; ligands; various growth and/or differentiation agents (e.g.,

epidermal growth factor, IGF-I, IGF-II, TGF-ß I-III, growth and differentiation factors, vascular endothelial growth factors, fibroblast growth factors, platelet derived growth factors, insulin derived growth factor and transforming growth factors, parathyroid hormone, parathyroid hormone related peptide, bFGF; $TGF_ß$ superfamily factors; BMP-2; BMP-4; BMP-6; BMP-12; sonic hedgehog; GDF5; GDF6; GDF8; PDGF); small molecules that affect the upregulation of specific growth factors; tenascin-C; hyaluronic acid; chondroitin sulfate; fibronectin; decorin; thromboelastin; thrombin-derived peptides; heparin-binding domains; heparin; heparan sulfate; DNA fragments and DNA plasmids . If other such substances have therapeutic value in the orthopaedic field, it is anticipated that at least some of these substances will have use in the present invention, and such substances should be included in the meaning of "bioactive agent" and "bioactive agents" unless expressly limited otherwise.

"Biologically derived agents" include one or more of the following: bone (autograft, allograft, and xenograft) and derivates of bone; cartilage (autograft, allograft, and xenograft), including, for example, meniscal tissue, and derivatives; ligament (autograft, allograft, and xenograft) and derivatives; derivatives of intestinal tissue (autograft, allograft, and xenograft), including for example submucosa; derivatives of stomach tissue (autograft, allograft, and xenograft), including for example submucosa; derivatives of bladder tissue (autograft, allograft, and xenograft), including for example submucosa; derivatives of alimentary tissue (autograft, allograft, and xenograft), including for example submucosa; derivatives of respiratory tissue (autograft, allograft, and xenograft), including for example submucosa; derivatives of genital tissue (autograft, allograft, and xenograft), including for example submucosa; derivatives of liver tissue (autograft, allograft, and xenograft), including for example liver basement membrane; derivatives of skin (autograft, allograft, and xenograft); platelet rich plasma (PRP), platelet poor plasma, bone marrow aspirate, demineralized bone matrix, insulin derived growth factor, whole blood, fibrin and blood clot. Purified ECM and other collagen sources are also intended to be included within "biologically derived agents." If other such substances have therapeutic value in the orthopaedic field, it is anticipated that at least some of these substances will have use in the present invention, and such substances should be included in the meaning of "biologically derived agent" and "biologically derived agents" unless expressly limited otherwise.

naturally occurring extracellular matrix, fibrin, blood clot and platelet rich plasma (PRP) disposed within the space.

Yet another aspect of this disclosure is a composite device for insertion into a space in a knee meniscus from which space a meniscus portion has been removed, the device comprising an upper cover made from a toughened sheet of naturally occurring extracellular matrix (ECM), the cover defining therebelow a space, and a mass comprising comminuted naturally occurring ECM disposed in the space.

Still another aspect of this disclosure is a plug to be inserted into an opening formed in a knee meniscus, the plug comprising a mass of comminuted naturally occurring ECM formed into the shape of a plug.

A further aspect of this disclosure is a device for repairing a tear in a knee meniscus, the device comprising strips of naturally occurring extracellular matrix laminated together to form a body portion and at least one extension portion extending away from the body portion, the body portion being shaped to be pulled by the extension portion into the tear to extend along and fill the tear.

Moreover, an additional aspect of this disclosure is a device for regenerating a meniscus or a portion thereof, the device comprising a wedge-shaped body having an upper panel and a lower panel angularly separated to define an apex portion and a base portion, the panels being formed of a naturally occurring extracellular matrix, and a support structure disposed between the upper panel and lower panel, the support structure comprising one or more members of rigid and hardened naturally occurring extracellular matrix.

One more aspect of this disclosure is an implantable device for repairing or regenerating at least a portion of a meniscus of a knee, the device comprising a toughened laminate including layers of ECM, the layers of ECM being toughened by a method selected from the group consisting of: compressing the layers of ECM together with heat to form the toughened laminate; compressing the layers of ECM together with vacuum to form the toughened laminate; compressing the layers of ECM together with pressure to form the toughened laminate; mechanically pressing the layers of ECM together while heating the layers to form the toughened laminate; and cross-linking the ECM laminate.

Still another aspect of this disclosure is an implantable device for repairing or regenerating at least a portion of a meniscus of a knee, the device comprising a toughened outer surface and a mass of biological material to provide a framework for meniscus regeneration, at least part of the mass of biological material being covered by the toughened outer surface.

Yet another aspect of this disclosure is an implantable device for repairing or regenerating at least a portion of a meniscus of a knee, the device comprising a wedge-shaped body having an upper panel and a lower panel angularly separated to define an apex portion and a base portion, at least part of the device comprising naturally occurring ECM.

In an additional aspect of this disclosure an implantable device is provided for regenerating at least a portion of a meniscus of a knee, the device comprising a cover sheet and a mass of biological material, the cover sheet extending over and beyond the mass of biological material.

Yet another aspect of this disclosure is an implantable device for regenerating at least a portion of a meniscus of a knee, the device comprising a plurality of surfaces defining compartments, a mass of biological material in each compartment, and a cover extending over the compartments and masses of biological material.

Still another aspect of this disclosure is an implantable device for regenerating at least a portion of a meniscus of a knee, the device comprising at least two adjacent materials having different densities, wherein each of the materials comprises ECM, wherein at least one of the material is treated to increase its density.

An additional aspect of this disclosure is an implantable device for repairing or regenerating at least a portion of vertebrate tissue, the device comprising a sheet of naturally occurring ECM having a density of at least 0.9 gm/cm^3.

One more aspect of this disclosure is an implantable device for repairing or regenerating at least a portion of a meniscus of a knee, the device comprising a toughened laminate including layers of naturally occurring bioremodelable collageneous matrix, the laminate being toughened by a method selected from the group consisting of: compressing the layers of naturally occurring bioremodelable collageneous matrix together with heat to form the toughened laminate; compressing the layers of naturally occurring bioremodelable collageneous

matrix together with vacuum to form the toughened laminate; compressing the layers of naturally occurring bioremodelable collageneous matrix together with pressure to form the toughened laminate; mechanically pressing the layers of naturally occurring bioremodelable collageneous matrix together while heating the layers to form the toughened laminate; and cross-linking the naturally occurring bioremodelable collageneous matrix laminate.

A final aspect of this disclosure is an implantable device for repairing or regenerating at least a portion of vertebrate tissue, the device comprising a sheet of naturally occurring bioremodelable collageneous matrix toughened to have a density of at least 0.9 gm/cm^3.

The above and other features of the present disclosure will become apparent from the following description and the attached drawings.

BRIEF DESCRIPTION OF THE DRAWINGS:

In the drawings:

Fig. 1 is a diagrammatical view showing a tibial platform with a typical meniscus structure on the platform and a portion of the meniscus removed for illustration purposes, the tibia platform being below the condyles of the femur;

Fig. 2 is a view looking down at the tibial platform and showing diagrammatically the insertion of an illustrative meniscus repair device to replace the portion of the meniscus removed;

Fig. 3 shows the inserted device in a position to be attached to the portions of the meniscus remaining after the injured portion is removed;

Fig. 4 is a sectional view taken from Fig. 3 along the lines 4-4;

Fig. 5 is a perspective view showing an open wedge-shaped device comprising an upper panel and a lower panel angularly separated to define an apex portion and a base portion;

Fig. 6 shows a wedge shaped device prior to folding with a pocket shown in imaginary lines formed in the device;

Fig. 7 shows a further step in the process in making the device shown in Fig. 6 to produce a filled, wedge-shaped device;

Fig. 8 shows an illustrative system and process for forming a pocket in a wedge-shaped device and filling that pocket with a biological material to promote meniscus regeneration;

Fig. 9 is a sectional view of a portion of Fig. 8 showing how the cavity is formed in the lower panel of the wedge-shaped device;

Fig. 10 shows the cavity filled with a biological material to regenerate the meniscus;

Fig. 11 shows how the upper cover for the pocket or upper panel is formed in the system illustrated in Fig. 8;

Fig. 12 is a sectional view showing the completed device made in the system shown in Figs. 8-11;

Fig. 13 shows a mechanism for forming radially extending compartments in the wedge-shaped device;

Fig. 14 shows a sheet of material formed in the Fig. 13 system with an elongated channels which will be interdigitated when the sheet is folded about a line defining the apex of the wedge;

Fig. 15 shows the folding of the formed sheet from Fig. 14;

Fig. 16 shows a sectional view taken along the lines 16-16 in Fig. 15 and showing the interdigitated channels being filled with a biological material to promote meniscus regeneration;

Fig. 17 shows an illustrative system for forming sheets of material such as SIS material into a wedge-shaped body;

Fig. 18 shows a sectional view taken along the line 18-18 in Fig. 17 to show how the system of Fig. 17 works to form a wedge-shaped device;

Fig. 19 shows a wedge-shaped device of the type produced by the system shown in Fig. 17 having an upper panel and a lower panel joined at an apex;

Fig. 20 shows how individual compartments may be formed from sheets of material such as SIS;

Fig. 20A shows a plurality of mandrels about which SIS is wrapped to form a plurality of channels;

Fig. 21 shows a single cylindrically shaped compartment of the SIS material;

Fig. 22 shows a plurality of such cylindrical compartments extending in a circumferential direction (about the meniscus) with the radially outer compartments being larger then the radially inner compartments and with the compartments contained within a sheet of SIS formed to cover the compartments, the compartments being filled with a biological material such as comminuted SIS;

Fig. 22A shows an illustrative method for forming several cylindrical channels together.

Fig. 22B shows the device of Fig. 22A filled with biological material such as comminuted SIS;

Fig. 23 shows a device made in accordance with Fig. 22;

Fig. 24 shows the device of Fig. 23 installed to replace a segment of a meniscus;

Fig. 25 shows an approach for wrapping a material such as SIS around a conical mandrel to form a single conical compartment;

Fig. 26 shows a plurality of conical compartments assembled together;

Fig. 27 shows such a conical compartment being filled with a material such as comminuted SIS;

Fig. 28 shows the compartment of Fig. 27 filled with the comminuted SIS;

Fig. 29 shows a plurality of such conical compartments arranged together between an upper panel and a lower panel of ECM material, the compartments extending radially inwardly from the base to the apex of the wedge-shaped device formed by the plurality of conical compartments;

Fig. 30 shows a sectional view taken along the line 30-30 in Fig. 29;

Fig. 31 shows a sectional view taken along the line of 31-31 in Fig. 30;

Fig. 32 shows a device containing a plurality of radially extending, generally triangular cross-section compartments;

Fig. 33 shows a method for forming the device structure shown in Fig. 32, essentially a plurality of triangular recesses to be formed together;

Fig. 34 shows the structure of Fig. 33 after the compartments are filled with material;

Fig. 35 shows a partial section of the Fig. 34 structure with radially extending compartments filled with comminuted SIS;

Fig. 36 shows the formation of a wedge-shaped pocket in a panel of SIS to be folded about an apex;

Fig. 37 shows the pocket in Fig. 36 filled with a material such as comminuted SIS with a portion of the panel closing the pocket;

Fig. 38 shows the bottom of the Fig. 36 and Fig. 37 structure;

Fig. 39 shows the structure of Figs. 36-38 attached to a meniscus;

Fig. 40 shows an ECM pillow in the shape of a portion of the meniscus with the end-tabs for attaching the pillow to the surrounding tissue;

Fig. 41 shows the device of Fig. 40 attached to a meniscus;

Fig. 42 shows a system for forming a multi-layered device with a central pocket or body portion containing a material such as comminuted SIS;

Fig. 43 shows the system of Fig. 42 closed to press the layers of material together enclosing the comminuted SIS;

Fig. 44 shows how the device of Figs. 42 and 43 may be installed into a meniscus;

Figs. 44A, 44B, and 44C show the process started in Fig. 44;

Fig. 45 shows a forming press similar to that of Figs. 42 and 43 except that there are a plurality of pockets of comminuted SIS separated from each other so that the device can be trimmed between the pockets;

Fig. 46 shows the press of Fig. 45 closed;

Fig. 47 shows how the device resulting from Figs. 45 and 46 may be installed on a tibial platform;

Fig. 47a shows a further step in the process started in Fig. 47;

Fig. 48 shows a side view of one of a plurality of ECM members which may be assembled together to fill and repair a cut-out opening in a meniscus;

Fig. 49 shows a plurality of members of Fig. 48 arranged and held together for insertion into a cut-out portion of the meniscus;

Fig. 50 shows the assembly of Fig. 49 held in place in the meniscus with a suture strand;

Fig. 51 is a perspective view of a framework structure made by hardened and toughened ECM members to form a lattice which defines spaces to be filled by ECM and which may be covered by ECM;

Fig. 52 shows a member of the lattice structure of Fig. 51;

Fig. 53 shows the device of Fig. 51 after being covered with ECM material;

Fig. 54 shows a view of the device of Figs. 51 and 53 inserted into the meniscus;

Fig. 55 shows a sectional view taken along the lines of 55-55 in Fig. 54;

Fig. 56 is a top view of a device similar to that shown in Fig. 38, except having barbs for attachment;

Fig. 57 is a top view of a device similar to that shown in Fig. 56, except having sutures for attachment; and

Fig. 58 is a perspective, partially cut-away view of a meniscus with the device of Fig. 56 inserted into the meniscus.

Fig. 59 shows another embodiment of a generally wedge-shaped implantable device, shown in position in a meniscus, the meniscus shown in cross-section;

Fig. 60 is a top plan view of the embodiment of Fig. 59 in position in the meniscus;

Fig. 61 is a top view of a device similar to those shown in Figs. 56 and 57, except the device lacks a pillow of biological material; and

Fig. 62 is a cross-section showing the device of Fig. 61 in place covering a cavity left by a partial menisectomy, with a discrete mass of biological material separately placed in the cavity.

DETAILED DESCRIPTION OF THE DRAWINGS

Referring to Fig. 1, it will be seen that a tibial platform 10 below the condyles 12 of a knee support a meniscus 11 from which an illustrative defective portion 14 is removed to leave a wedge-shaped space 16. In the removal process, the surgeon will generally leave an outer rim 18 of the meniscus. It is well known that the radially outer portion of a meniscus is richly vascularized while the radially inner portion of a meniscus is not so well vascularized. Menisci have been described by people working in the orthopaedic field to be two semi-lunar, wedge-shaped concave fibrocartilagenous structures anchored to the tibia plateau (such as shown at 10) in the knee. The menisci provide a large surface of articulation between the otherwise

incongruent surfaces of the tibia platform or plateau and the femur condyles (such indicated at 12). The menisci serve to reduce contact stresses and wear in the knee joint. The peripheral rim of the meniscus at the menisco-synovial junction is highly vascular (red zone) whereas the inner two-third portion of the meniscus is completely avascular (white zone), with a small transition (red-white zone) between the two. Degenerative or traumatic tears to the meniscus which result in partial or complete loss of function frequently occur in the white zone. Such tears result in unstable flaps of meniscal tissue in the knee joint causing, in the short term, severe joint pain and locking, and in the long term, a loss of meniscal function leading to osteoarthritis. The current standard of care involves partial menisectomy to remove unstable tissue to relieve joint pain and locking. However, when the resected tissue is from the avascular (white zone), the meniscus has little potential for self regeneration. Thus, the current standard of care results in partial but permanent loss of meniscal tissue, making the joint susceptible to osteoarthritis.

The portion 14 removed from the structure shown in Fig. 1 includes a portion of the original meniscus which is within the avascular zone, particularly the radially inner portion.

Fig. 2 shows how a device 20 made in accordance with the present invention may illustratively be inserted into the space 16 to be against the outer rim 18. This illustrative device 20 is shown in Figs. 3 and 4 in position filling the space 16 and against the rim 18 left by the surgeon. Fig. 4 shows the device as comprising an upper cover or upper panel 22 and a lower cover or lower panel 24. These panels 22, 24, which may illustratively be angularly related, will define an internal space 26 between the covers. Internal space 26 may be filled with a biological material or a biological structure providing a framework for regeneration of the meniscus into the space 16.

Figs. 1-4, therefore, show the general concept of the present invention in which a generally wedge-shaped device 20 is inserted into the knee to fill a space 16 from which a defective portion of a meniscus has been removed. Fig. 2 suggests that the device 20 may be inserted, for example, in arthroscopic surgery through portals provided in the outer anterior surface of the knee opening into the knee cavity between the condyles 12 and the tibial platform 10. It will be appreciated that the device 20 will be inserted downwardly and inwardly through an opening to be placed

into the space 16. It will also be appreciated that the device 20 may be anchored in some fashion in the space 16 such that it is in contact with the boundaries of the space as suggested in Figs. 3 and 4. The upper cover 22 of the device 20 will serve as a bearing surface for the condyle 12 disposed thereabove and be subjected to the compression and stress forces involved in articulation of the knee. The condyle will move upon the upper surface of the cover 22. The device 20 will serve as a cushion or pillow for handling the compression load provided by the knee.

Turning to Figs. 5, 6 and 7, it will be seen that an illustrative concept of a regeneration device is somewhat diagrammatically illustrated. The illustrative device 30 includes an upper panel 32 and a lower panel 34 defining a wedge-shaped device having a base portion 36 and an apex portion 38. The device 30 illustrated in Figs. 5, 6 and 7 illustrates that a plurality of layers of a naturally occurring ECM such as SIS may be layered together and formed to provide a generally wedge-shaped device. Fig. 6 suggests that the device may include a formed cavity 39 (illustrated in phantom) and that the device may be folded about a fold line 40 to provide a device such as indicated at 42 in Fig. 7. While the Fig. 5 device 30 suggests an open wedge-shaped design, the device 42 in Fig. 7 suggests that, between the upper and lower panels 32, 34 a pocket of biological material may be disposed. In Fig. 6, a plurality of tacks 44 are shown attached to one of the two panels of the device to be used for securing the device to surrounding tissue in the knee. The panels 32, 34 may be trimmed to the desired wedge shape.

Fig. 8 shows diagrammatically an illustrative system for forming devices similar to that shown in Figs. 6 and 7, and Figs. 9, 10, 11 and 12 show the stages of the system of Fig. 8. The illustrative Fig. 8 system comprises a vacuum plate or platen 50 having a cavity 52 in the shape of the desired device with a vacuum pump such as indicated at pump 54 connected to the cavity 52 by a tube 56. It will be appreciated that the cavity 52 is provided with a plurality of openings leading to a manifold space within the platen 50 which is connected to the pump 54. Several layers 58 of a naturally occurring ECM such as SIS are placed on the plate 50. These layers 58 which are moist and flexible are pulled by vacuum down into the cavity 52 to form a recess for receiving a mass of biological material 60 which will take the shape indicated at 62 defined by the cavity 52. Once the layers 58 are pulled into the cavity 52, and the mass 60 is placed in the shaped opening formed in the layers 58 by

While the Fig. 8 illustration shows four layers 58 and six layers 64, it will be appreciated that different numbers of layers may be used. For example, a device may have from 2 to 10 layers 58 and from 5 to 20 layers 64. It will also be appreciated that different numbers of layers, different orientations of the layers, and different drying conditions may affect toughness. In one example, strips of clean, disinfected porcine SIS material as described in U.S. Patents Nos. 4,902,508 and 4,956,178, were cut into swatches approximately 3.5" square. Several 20-layer implants were assembled from the swatches. Each swatch was oriented at 72° from the previous to obtain an isotropic laminated implant. The implants were dried under vacuum pressure in a gel drier system (Model FB-GD-45, Fisher scientific, Pittsburgh, PA), for approximately 2 hours at 30°C, under two different conditions. One set of implants was sandwiched between perforated stainless steel screens (20 gage thick 304 stainless steel, 15"x19" screen with 1/16" holes, 3/32" staggered centers arranged in hexagonal-close-packed format). These implants had a "dimpled" surface after drying, corresponding to the perforations on the screen. The other set of implants were dried in the same way as the first except that the porous screens were replaced by flat non-perforated surfaces. These implants had a smooth surface after drying. At least six implants of each type were fabricated. Uniaxial tension mechanical testing of implants, conducted according to ASTM standard D638, showed that the average failure stress of the smooth implants was more than two times that of the dimpled implants (46.02 +/- 1.14 MPa versus 19.97 +/- 1.04 MPa.) The smooth implants were hence tougher than the dimpled implants.

The sequence of the system of Fig. 8 is illustrated showing the layers 58 drawn down into the cavity 52 in Fig. 9. Fig. 10 shows the mass 60 located in the cavity and Fig. 11 shows the platen 70 closing against the platen 50 to capture the layers 64 above the mass 60.

As discussed above, a naturally occurring ECM for use in this invention is SIS. While SIS is commercially available, an illustrative method of obtaining SIS is as follows. Porcine SIS preferably comes from pigs raised on a Specific Pathogen Free farm. Such pigs are free from all pneumonia, diarrhea, lice, mange, and dysentery. The average pig weight is 220-280 lbs (100-127 kg). The age of each pig should be between 150-200 days, and each pig is free from antibiotic administration for 21 days before slaughter. It is preferable that no unrefined animal

byproducts be included in the pigs' diets. The SIS is obtained from the slaughterhouse by standard methods of obtaining casings. However, unless the SIS is used immediately, it is preferred that the SIS be stored in a frozen state lower than 20°C, and most preferably at -80°C. The SIS may be cleaned and disinfected by standard techniques, for example with 20% ethanol and .15% peracetic acid.

Fig. 12 shows the illustrated resulting device 80 which has a base portion 82, an apex portion 84, an upper cover 86, and a lower cover 88. The mass 60 is disposed between the covers 86, 88. Illustratively, the layers 58 and 64 may be layers or strips of SIS while the mass 60 may be a mass of comminuted SIS. In various embodiments of the device 80, and other illustrative devices hereinafter, the mass 60 may be or may comprise materials such as bioactive agents, biologically derived agents, cells, biologically compatible inorganic materials, biologically compatible polymers, and/or combinations of such materials. In a preferred method, the SIS is comminuted at 9391 rpm using a Comitrol® Processor Model 1700 with cutting head 140084-10 and a Vericut, sealed impeller from Urschel Laboratories Inc. (Valparaiso, Indiana). This method produces comminuted SIS of a consistent and reproducible size.

The device formed under pressure, compression, and heat in the system shown in Fig. 8 may be further treated in well known lyophilization processes to dry the device for shipment and/or storage. The lower surface 88 and the base portion 82 may be perforated as by penetration with a very fine cannula or other means to facilitate the hydration of the device. It will be appreciated that, when the wet layers of SIS 58, 64 and the mass 60 are dried, the body of the device, particularly the lower cover 88 and base portion 82 may shrink or cave in without the moisture. However, as illustrated, that shrinkage or caving in does not occur. The pinholes indicated at 90 expedite the hydration of the device for use by the physician.

Laminating the layers 64 under heat and pressure will provide a toughened surface to serve as a bearing surface against which a condyle will move. Ultimately, after insertion into the knee, and over a period of time, the device 80 will be remodeled to regenerate the damaged portion of the meniscus. Illustratively, subsequent to insertion, the patient will recuperate for 3-6 weeks without substantial load bearing on the knee. During this time, body fluids such as blood and synovial fluids infuse into the implant. If additional biological lubricants such as hyaluronic

acid are injected into the site, such injected fluids also infuse into the implant. Other lubricants could also be used in addition to or alternatively from hyaluronic acid: lubricin, articular cartilage surface zone proteins, synovial fluid, surface-active phospholipids, and lubricating glycoprotein I, II, or any combination thereof, for example. The cells that infuse into the implant are known to proliferate in mass 60. Subsequently, when the patient resumes load bearing on the knee, it is believed that the cells begin secreting structural proteins (mostly collagens) in response to exposure to the forces of load bearing. These secreted structural proteins reform the meniscal body. It is believed that layers 64 eventually abrade away due to mechanical shearing or due to bioabsorption.

The device 80, therefore, is a composite device comprising layers of naturally occurring ECM material treated to provide a bearing surface and additional ECM material positioned below that surface to provide a framework into which regeneration of the meniscus occurs.

Figs. 13-16 show another system for fabricating a device 100 which comprises panels 102 and 104 that can be folded together about a line 106 to provide an upper cover and a lower cover with radially extending channels or compartments disposed therebetween. Illustratively, a vacuum plate or manifold 110 is provided for connecting to a pump 112 with a plurality of cavities 114, 116, 118, 120, 122 formed in the platen 110, each cavity being a radially extending, somewhat conical trough deeper and larger at its radially outer end, radially outwardly from the apex fold line 106. Wet layers of ECM strip are placed over the platen 110 and a vacuum is pulled sucking portions of the layers down into the cavities 114, 116, 118, 120, 122. Additional layers of ECM material may then be placed over the cavities. The resulting pressed and formed product is shown in Fig. 14 including the panels 102, 104 formed about a bend line 106. Each panel 102, 104 carries compartments that may be filled with comminuted ECM. Each of the three cavities 114, 116, 118 provide compartments 115, 117, 119. The cavities 120 and 122 provide the compartments 121 and 123. Since the compartments 115, 117, 119, 121, 123 are smaller adjacent the fold line 106 and larger radially outwardly from the fold line, when the two panels 102, 104 are folded together along bend line 106, the resulting product 100 will be a generally wedge-shaped device as illustrated in Fig. 15. The compartments 115, 117, 119, 121, 123 are spaced apart so that they will be

interdigitated as shown best in Fig. 16 when the panels 102, 104 are folded. The upper panel (shown as 102) may be provided with tacks as indicated at 130 for attachment of the device 100 to the surrounding tissue. The compartments 115, 117, 119, 121, 123 will be generally radially extending in the device from the radially outer portion of the device as it is installed in a meniscus with the larger ends of the compartments configured to direct the regeneration radially inwardly. It will be appreciated that the compartments may be perforated and that the lower cover of the device may also be perforated to facilitate hydration of the product after it is delivered to the surgeon. The device 100 may be cut by the surgeon as indicated by the cut line 125 in Fig. 16 to make the device smaller in the circumferential direction of the meniscus.

It will be appreciated that tacks 130 may be made from well known materials that dissolve or absorb over time in the body. Such materials include, but are not limited to, PLA, PGA, a PLA-PGA copolymer, etc. In addition, as disclosed in U.S. Patent Application "Unitary Surgical Device and Method" (Attorney Docket No. DEP-750), filed concurrently and incorporated by reference herein, ECM can also be used for fixating elements like tacks 130.

Figs. 17, 18, and 19 show an illustrative system 140 comprising a male die system 142 and a female die system 144 for forming a plurality of layers of ECM material 146 into a desired shape. The illustrative system 140 has the male die system 142 and female die system 144 designed to produce a wedge-shape product 160. While the system 140 shown in Figs. 17 and 18 will not be described in great detail herein, it will be seen in from the drawings that the male die system 142 and female die system 144 may be clamped or otherwise held together to provide a mechanical compression force on the layers 146. While screws are illustrated to indicate that the two systems 142, 144 may be clamped together under desired pressure simply by tightening the screws, it will be appreciated that presses of various types may be used to provide mechanical compressive forces for a plurality of layers such as indicated at 146. In addition to the mechanical compression force, the system 140 may be constructed such that either the male die system 142 or the female system 144 may be constructed to provide vacuum or heated dry air for treating the layers 146. The male die system 142 may be provided with a source 150 of compressed air or, if desired, heated compressed air forced into the male die system 142. A plurality of openings

cavity in the meniscus, shown at 408 in Fig. 59, with portions 410, 412 of the meniscus left to lie over and under at least part of the device 400.

Figs. 42 and 43 show an illustrative diagrammatic system for fabricating a device 360 which is shown being installed to repair a meniscal tear in Figs. 44, 44A, 44B and 44C.

Illustratively, the device 360 may be shaped and formed as diagrammatically illustrated in Figs. 42 and 43. The illustrative die system comprises an upper die 364 and a lower die 366 with registering cavities 368 in the upper die and 370 in the lower die. A plurality of layers or strips of ECM material are used to fabricate the device 360. Illustratively, a plurality of layers 380 are placed over the cavity 370 as shown in Fig. 42. A mass of comminuted ECM 382 is placed in the position shown in Fig. 42 to go in the space between the die cavities 368, 370. At each end of the device, there are intermediate set of layers 384, 386. Then, an upper set of layers 388 of ECM material is provided over the layers 384, 386 and the mass 382. When the die halves 364, 366 are closed, as depicted in Fig. 43 a central body portion 390 of the device 360 is formed to have a mass of comminuted biological material surrounded by the upper layers 388 and the lower layers 380. A vacuum may be applied to the cavities 368, 370 through the lines 372, 374 or warm air may be provided through the lines. Once the device is formed as shown in Fig. 43, the central body portion 390 has extension portions 392, 394 formed by pressing the layers 380, 384, 386, 388 together. Either extension portion 392, 394 may be used by the surgeon to pull the device 360 into a tear such as indicated at 393 at Figs. 44, 44A, 44B, 44C. Essentially, a surgeon may use one of the extensions, such as extension 392, to pull the central body portion 390 downwardly into the tear 393 by extending the end of the extension 392 into the tear and then radially inwardly under the inner most edge of the meniscus. It will be appreciated that some surgeons may prefer to pull the extension 394 radially outwardly under the outer edge of the meniscus.

Figs. 44A, 44B and 44C show the progression of the insertion of the device 360 into the tear 393. A surgeon may cut away a portion of the device 360 which extends above the upper surface of the meniscus as suggested in Fig. 44C. Also, the surgeon may use a tack 396 to hold the distal end of the extension 392 in place as suggested in Fig. 44C.

generated by articulation of the condyle relative to the platform and a biological material below the cover to provide a framework for regenerating the meniscus.

65. An implant for regenerating a portion of a meniscus in the knee, the implant comprising an outer cover providing a cavity, an upper surface to face the femur of the knee and a lower surface to face the tibial platform of the knee, the cavity being disposed between the surfaces of the cover, the outer cover being formed from a material selected from the group consisting of SIS, stomach submucosa, bladder submucosa, alimentary submucosa, respiratory submucosa, genital submucosa, and liver basement membrane, the upper surface being toughened by cross-linking the collagen fibers, and the cavity being filled with a material selected from the group consisting of blood clots, fibrin, comminuted ECMs and PRP.

66. The implant of claim 65 in which the cavity is divided into a plurality of channels extending radially inwardly.

67. The implant of claim 65 in which the cavity is divided into a plurality of channels extending circumferentially.

68. An implant for regenerating a portion of a meniscus in a knee, the implant having a radially outer portion, a radially inner portion, an upper surface and a lower surface, the outer and inner portions being curved to conform to the outer and inner portions, respectively, of the portion of the meniscus to be regenerated, the implant having an outer shell defining the outer and inner portions and upper and lower surfaces, the outer shell being formed from naturally occurring extracellular matrix material, and at least the upper surface being toughened, the shell having a space therein, and a biological material disposed in the space to provide a framework for regenerating the meniscus.

69. An implant for regenerating a knee meniscus or a portion thereof, the implant having radially outer and inner portions corresponding to the radially outer and inner portions of the portion of the meniscus to be regenerated, and an outer shell providing an inner space extending from the outer portion to the inner portion, the outer shell having an upper surface to be engaged by the femur of the knee and a lower surface to be supported on the tibial platform of the knee, the outer shell being formed from a plurality of layers of SIS laminated together and treated to be toughened to withstand the shearing and compressive forces in the knee in vivo, and at least one material selected from the group consisting of fibrin, blood clots,

comminuted SIS and PRP disposed in the space to accommodate the meniscus regeneration.

70. A method for regenerating a portion of a knee meniscus having a radially outer portion and a radially inner portion, the meniscus portion extending circumferentially about a medial or a lateral portion of the tibial platform of the knee, the method comprising the steps of:

removing a segment of a meniscus to provide a meniscal space extending circumferentially about a predetermined portion of the tibial platform and leaving remaining segments of the original meniscus, the meniscal space having a radially outer portion and a radially inner portion,

providing an implant device constructed from a naturally occurring extracellular matrix to conform to the meniscal space and placing the device into the space, the device having a radially outer portion and a radially inner portion,

attaching the device to the adjacent tissue of the knee, and

encouraging in regeneration from the radially outer portion of the device to the radially inner portion of the device.

71. The method of claim 70 wherein the encouraging step comprises channeling blood flow from the radially outer portion of the device to the radially inner portion of the device.

72. The method of claim 70 wherein the device is provided with channels extending from the radially outer portion to the radially inner portion to encourage vascularization radially inwardly.

73. A method for regenerating a meniscus or a portion thereof comprising the steps of:

replacing a portion of an original meniscus with a naturally occurring extracellular matrix material shaped to conform to the meniscus portion removed, and

shaping the material such that in vivo the material defines channels extending from the radially outer portion of the meniscus to the radially inner portion of the meniscus to support the regeneration.

74. A method for regenerating a knee meniscus or a portion thereof comprising the steps of:

replacing a portion of an original meniscus with a naturally occurring extracellular matrix material shaped and formed to provide an upper surface

toughened to withstand the compression and shear stress of articulation of the knee and an interior space into which meniscal regeneration occurs, and

attaching the material to the surrounding tissue.

75. The method of claim 74 in which the interior space contains a material selected from the group consisting of a mass of comminuted naturally occurring extracellular matrix material, fibrin, blood clot and PRP .

76. The method of claim 74 in which the upper surface is toughened by dehydrothermal cross-linking.

77. A device for regenerating a removed portion of a knee meniscus, the device comprising a shell shaped conformingly to fit into the space occupied by the removed meniscus portion, the shell providing an upper surface to withstand the articulation of the knee and a space under the upper surface, and a biologically derived agent, said biologically derived agent comprising a material selected from the group consisting of comminuted naturally occurring extracellular matrix, fibrin, blood clot and platelet rich plasma (PRP) disposed within the space.

78. A composite device for insertion into a space in a knee meniscus from which space a meniscus portion has been removed, the device comprising an upper cover made from a toughened sheet of naturally occurring extracellular matrix (ECM), the cover defining therebelow a space, and a mass comprising comminuted naturally occurring ECM disposed in the space.

79. The device of claim 78 in which the mass also comprises a biologically derived agent.

80. The device of claim 78 in which the mass also comprises platelet rich plasma.

81. The device of claim 78 in which the mass comprises blood clot.

82. A plug to be inserted into an opening formed in a knee meniscus, the plug comprising a mass of comminuted naturally occurring ECM formed into the shape of a plug.

83. The plug of claim 82 in which the plug comprises a shell of a naturally occurring ECM sheet disposed about the mass.

84. A device for repairing a tear in a knee meniscus, the device comprising strips of naturally occurring extracellular matrix laminated together to form a body portion and at least one extension portion extending away from the body

portion, the body portion being shaped to be pulled by the extension portion into the tear to extend along and fill the tear.

85. The device of claim 84 in which the body portion comprises a mass of comminuted naturally occurring extracellular matrix captured between the strips.

86. The device of claim 84 in which the body portion is separated into a plurality of spaced apart compartments, and a mass of comminuted naturally occurring extracellular matrix disposed in each compartment, the device having a space between adjacent compartments to facilitate cutting the body between compartments to separate the body.

87. A device for regenerating a meniscus or a portion thereof, the device comprising

a wedge-shaped body having an upper panel and a lower panel angularly separated to define an apex portion and a base portion, the panels being formed of a naturally occurring extracellular matrix, and

a support structure disposed between the upper panel and lower panel, the support structure comprising one or more members of rigid and hardened naturally occurring extracellular matrix.

88. The device of claim 87 in which the one or more members comprise a plurality of generally wedge shaped members, each member having an upper edge supporting the upper panel and a lower edge supported on the lower panel.

89. The device of claim 87 in which the one or more members comprise a plurality of wafer-like members, each member having a generally wedge shape corresponding to a meniscus section taken from a natural meniscus in a plane extending radially outwardly and axially along the tibial axis, the plurality of members being disposed in a side-by-side relation about the circumference of the meniscus being generated between the upper and lower panels, each member having an upper edge supporting the upper panel and a lower edge resting on the lower panel.

90. The device of claim 89 in which the plurality of wafer-like members are connected together to allow some individual movement of each member.

91. The device of claim 89 in which each of the members is provided with an opening therethrough, and the device further comprises a connecting member extending through the openings in the members.

147. The implantable device of claim 142 further comprising at least one of the following: a bioactive agent; a biologically derived agent; cells; a biological lubricant; a biocompatible polymer; and a biocompatible inorganic material.

148. The implantable device of claim 142 further comprising at least one biologically compatible material associated with the mass of biological material, said biologically compatible material selected from the group consisting of: a bioactive agent; a biologically derived agent; cells; a biological lubricant; a biocompatible polymer; and a biocompatible inorganic material.

149. The implantable device of claim 142 wherein the cover sheet comprises a wedge-shaped body having an upper panel and a lower panel angularly separated to define an apex portion and a base portion.

150. The implantable device of claim 149 wherein the mass of biological material is positioned between the upper panel and lower panel.

151. The implantable device of claim 142 wherein the cover sheet has a toughness sufficient to at least temporarily withstand the forces of articulation at the knee without degrading.

152. The implantable device of claim 142 wherein the cover sheet comprises a laminate of ECM layers that have been toughened by a method selected from the group consisting of:

compressing the layers of ECM together with heat to form the toughened laminate;

compressing the layers of ECM together with vacuum to form the toughened laminate;

compressing the layers of ECM together with pressure to form the toughened laminate;

mechanically pressing the layers of ECM together while heating the layers to form the toughened laminate; and

cross-linking the ECM laminate.

153. The implantable device of claim 142 wherein the cover sheet has a density of at least 0.9 gm/cm^3.

154. The implantable device of claim 142 wherein the cover sheet is treated to increase its density.

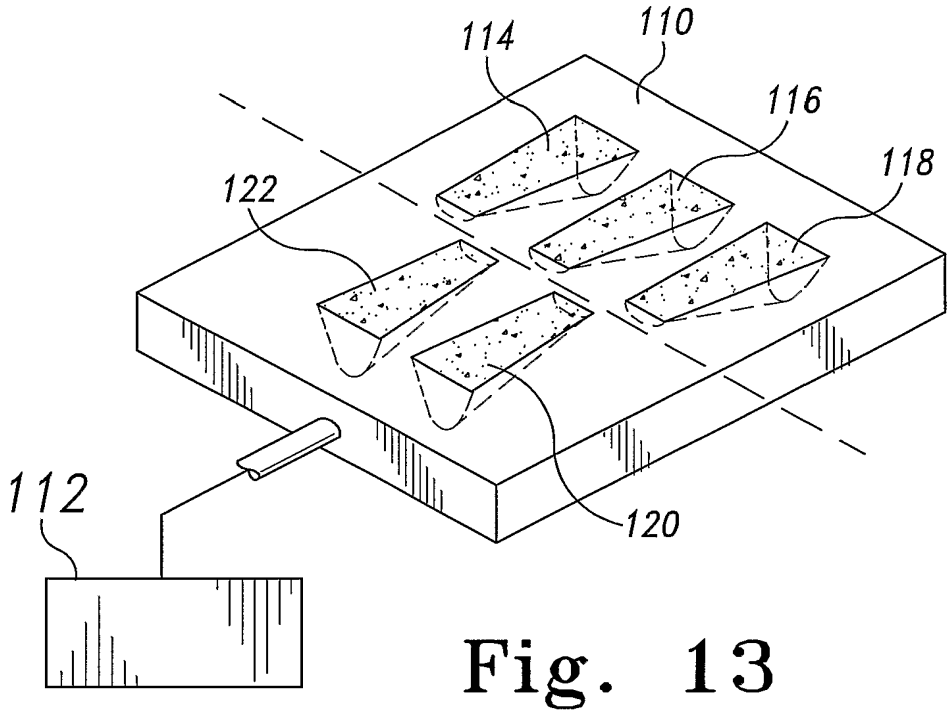

Fig. 13

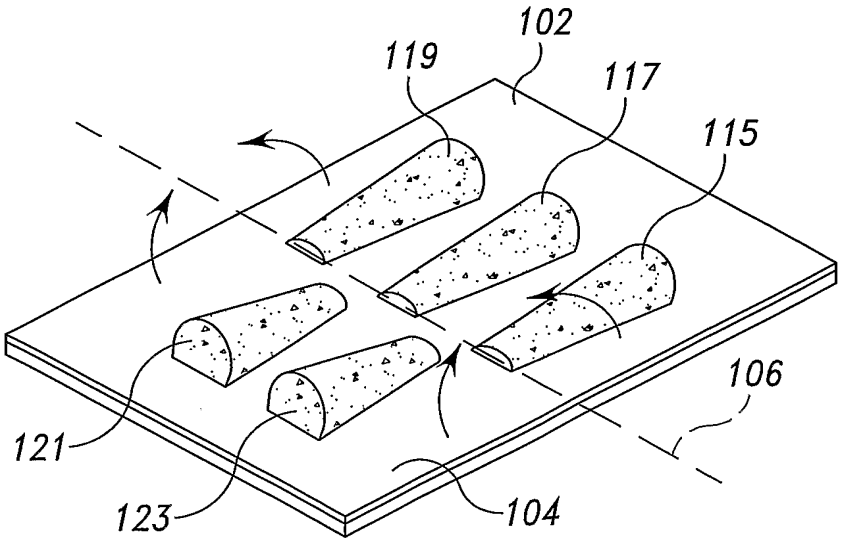

Fig. 14

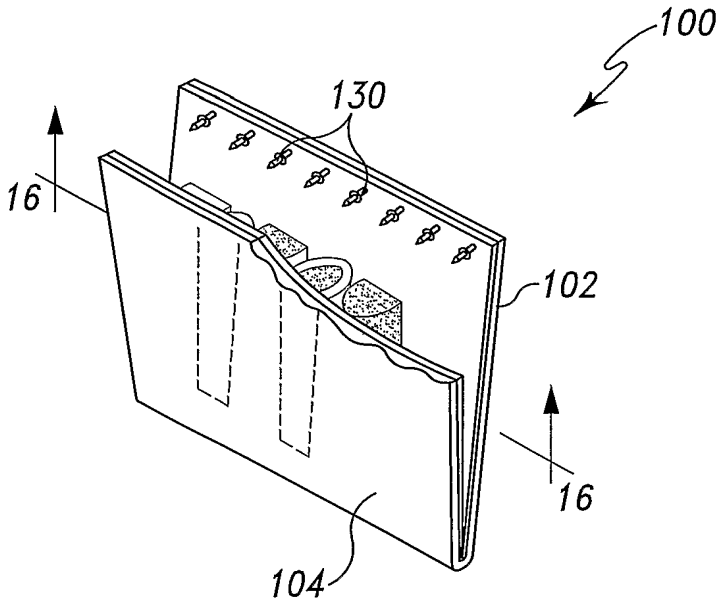

Fig. 15

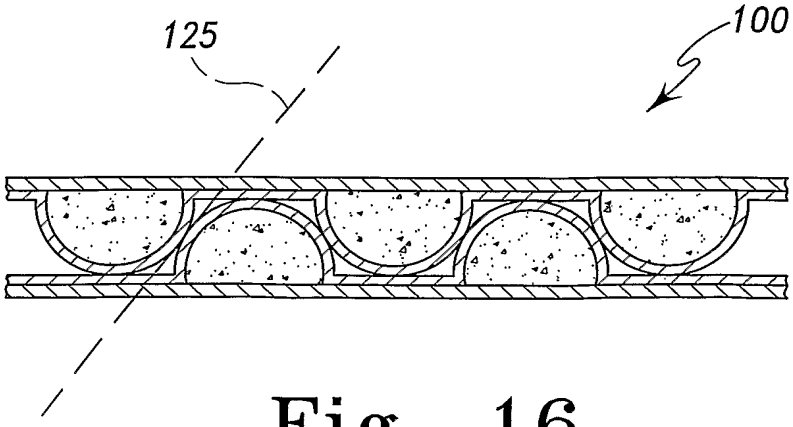

Fig. 16

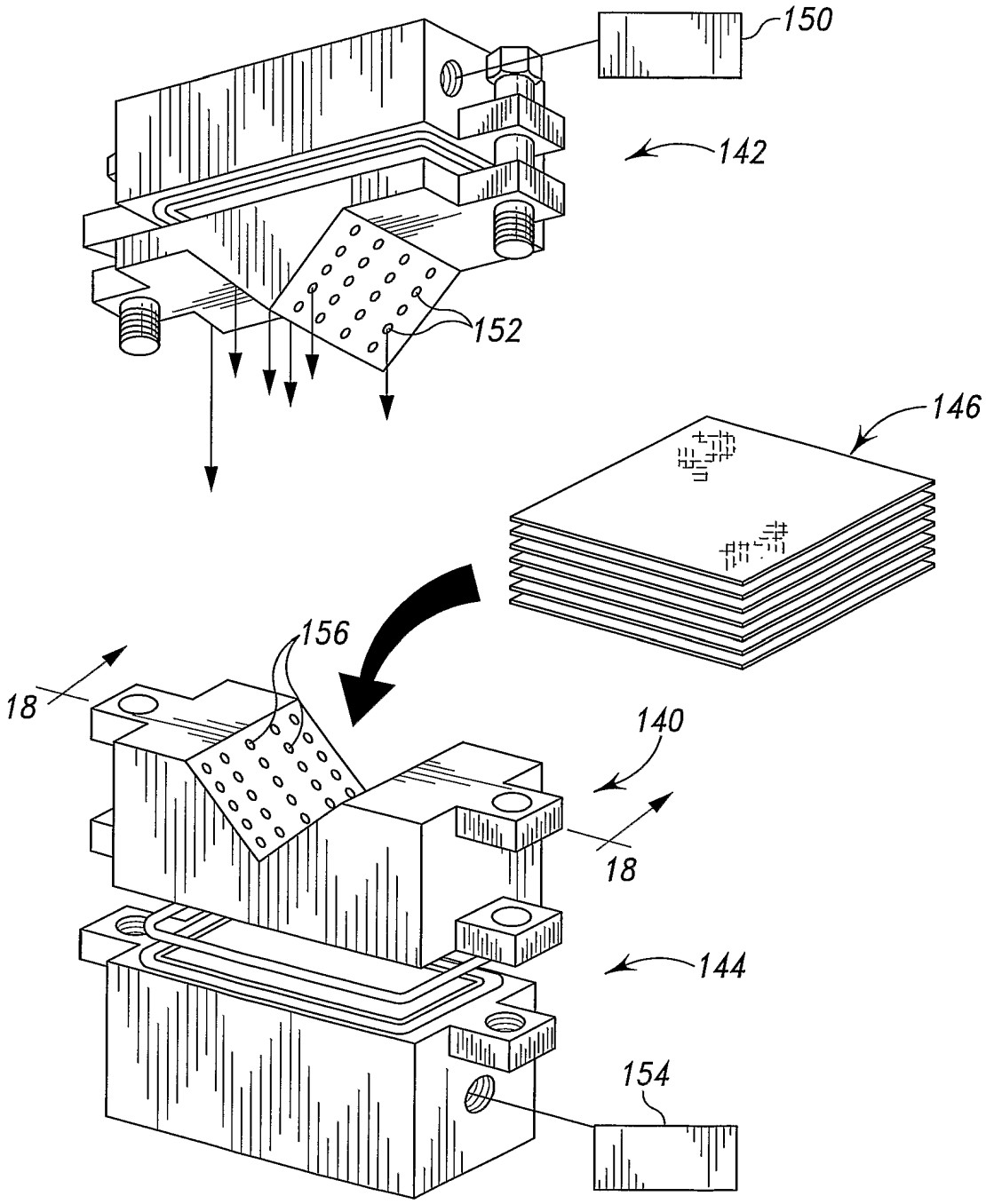

Fig. 17

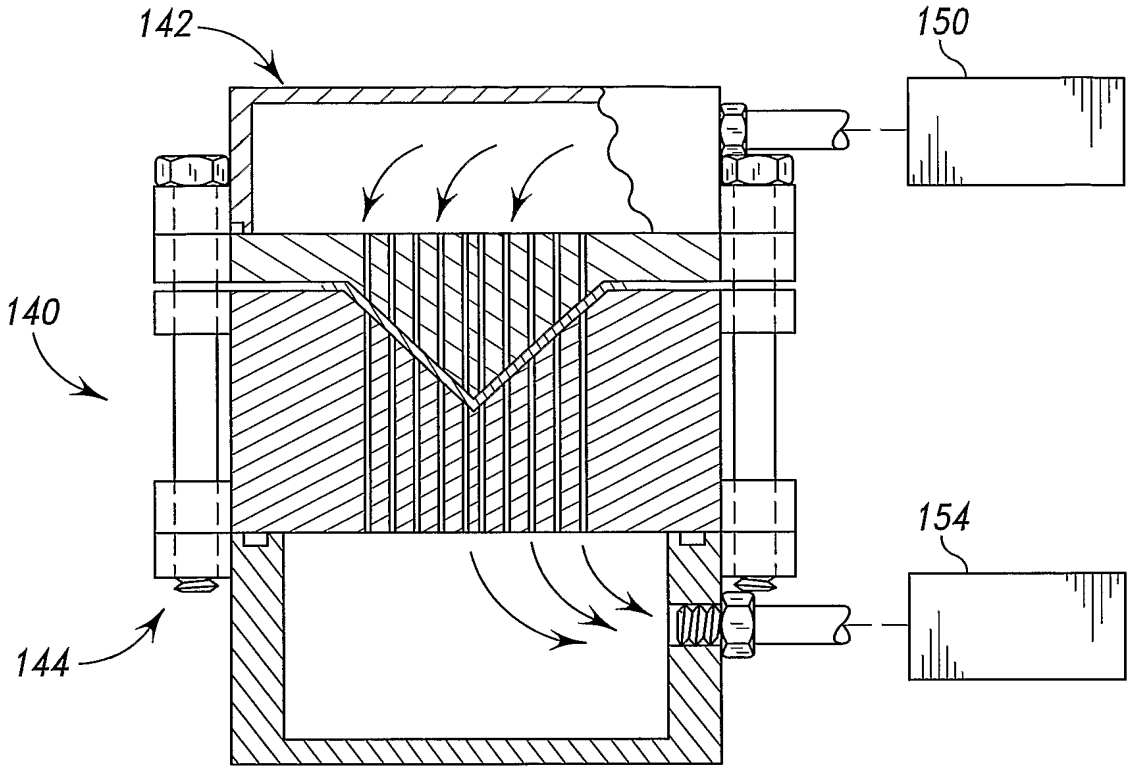

Fig. 18

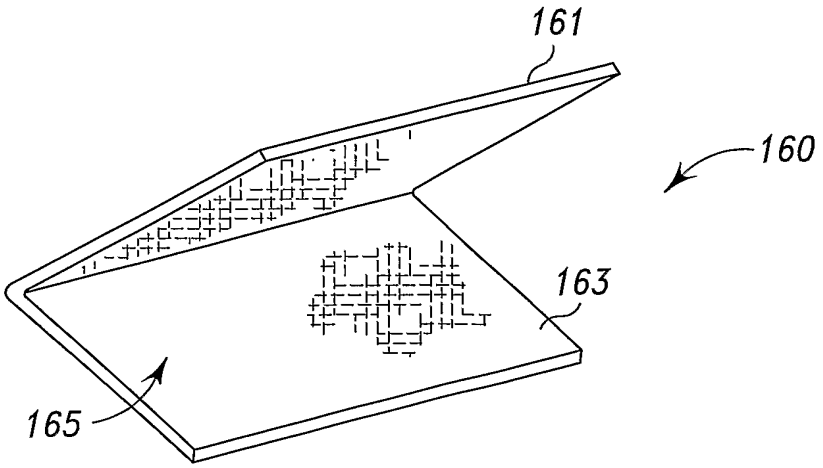

Fig. 19

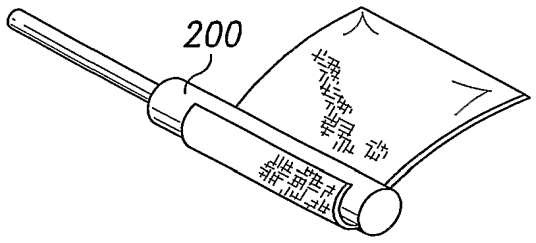

Fig. 20

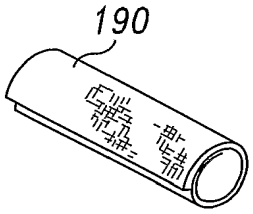

Fig. 21

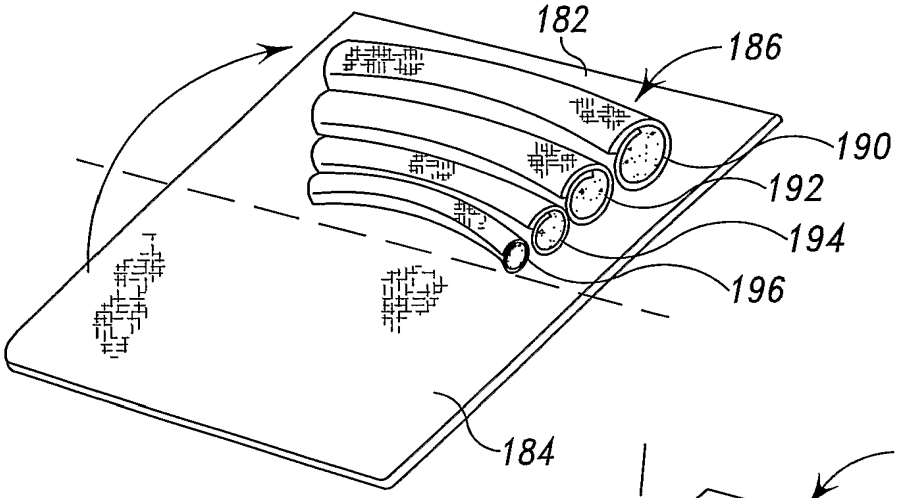

Fig. 22

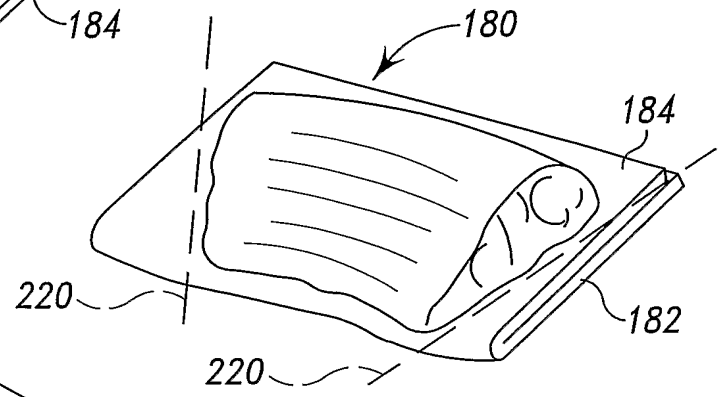

Fig. 23

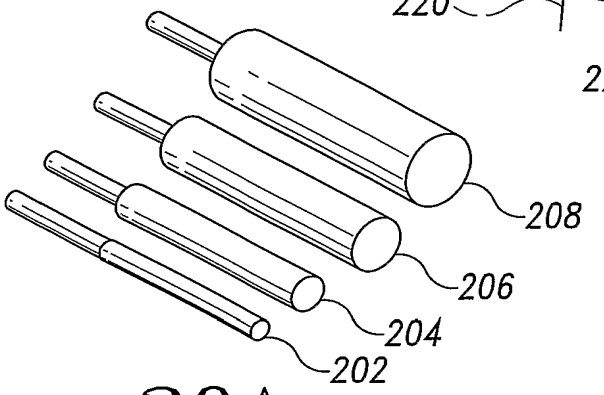

Fig. 20A

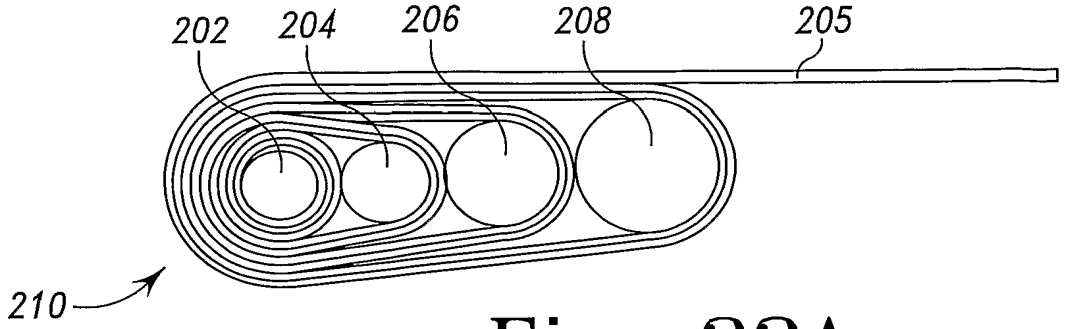

Fig. 22A

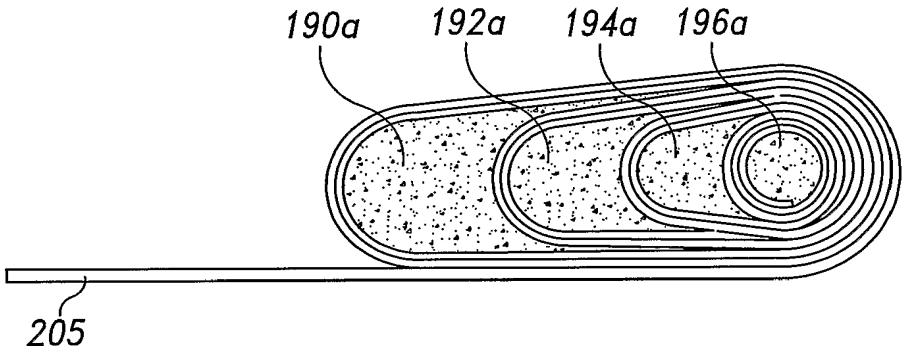

Fig. 22B

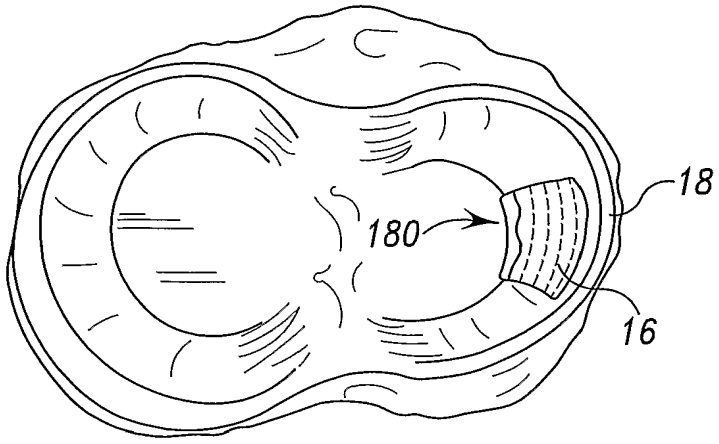

Fig. 24

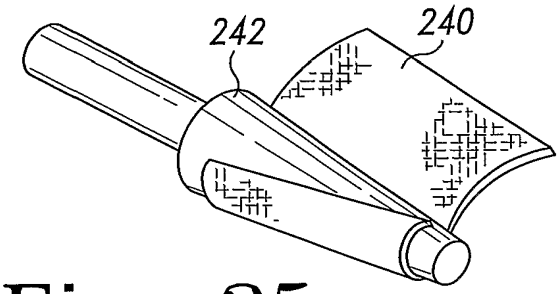

Fig. 25

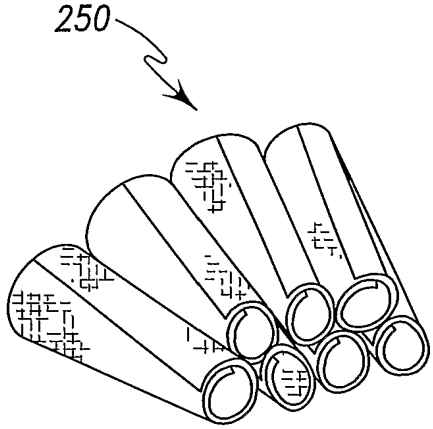

Fig. 26

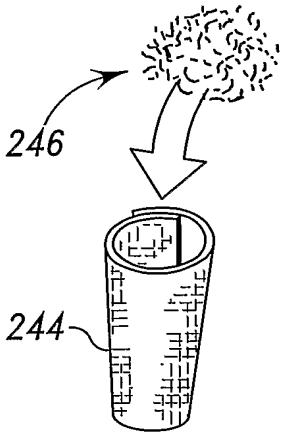

Fig. 27

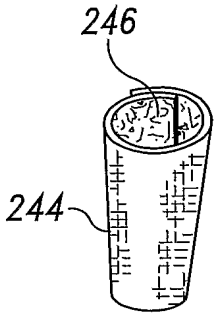

Fig. 28

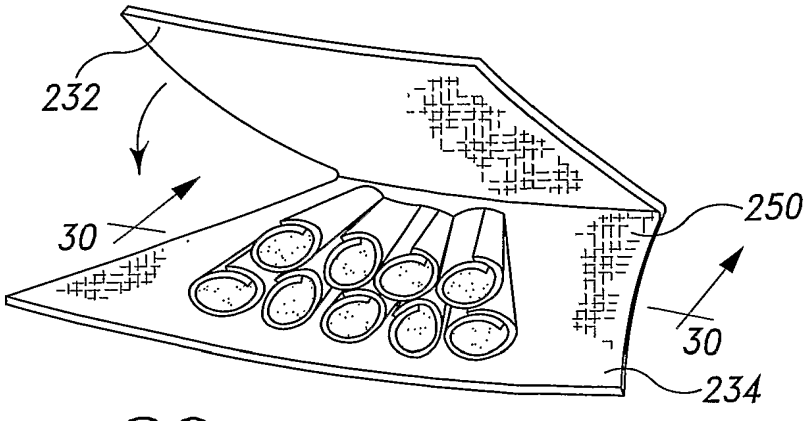

Fig. 29

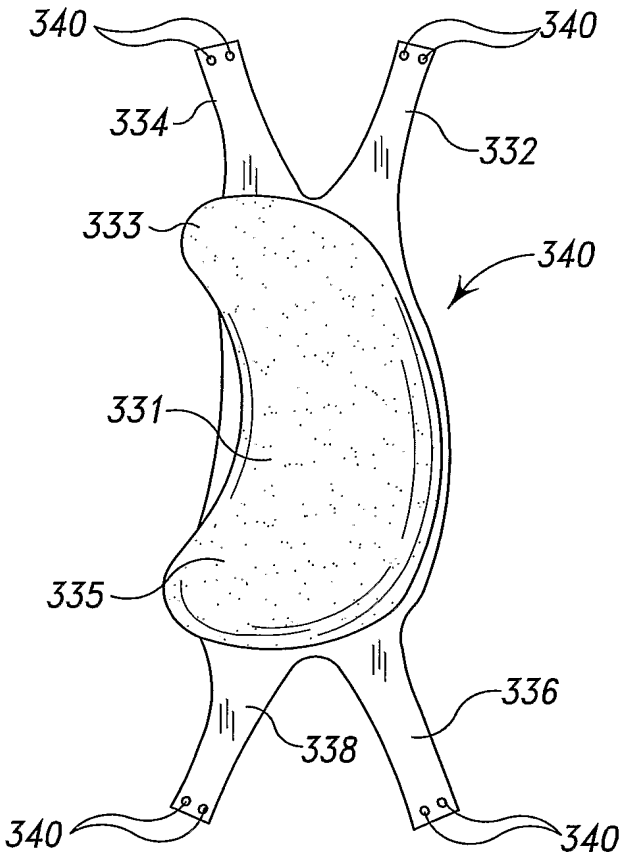

Fig. 40

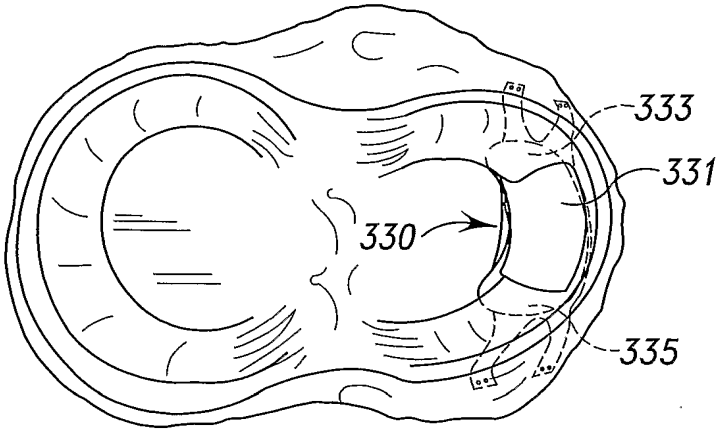

Fig. 41

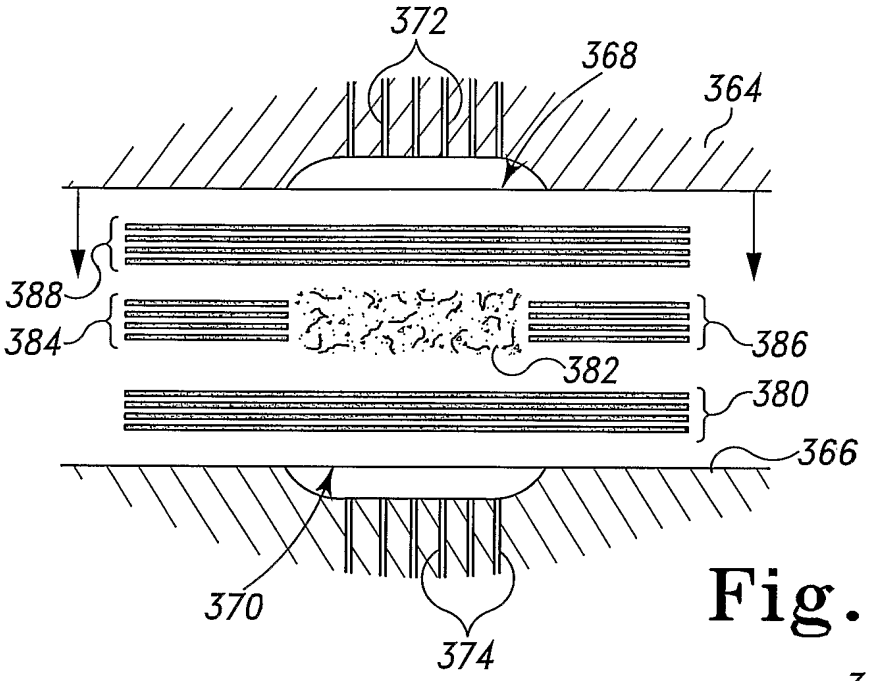

Fig. 42

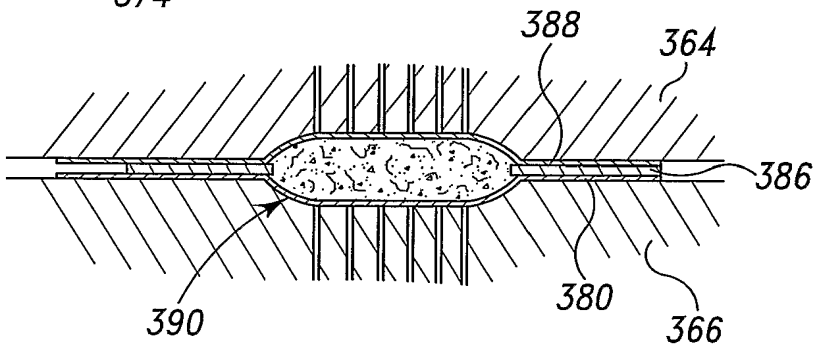

Fig. 43

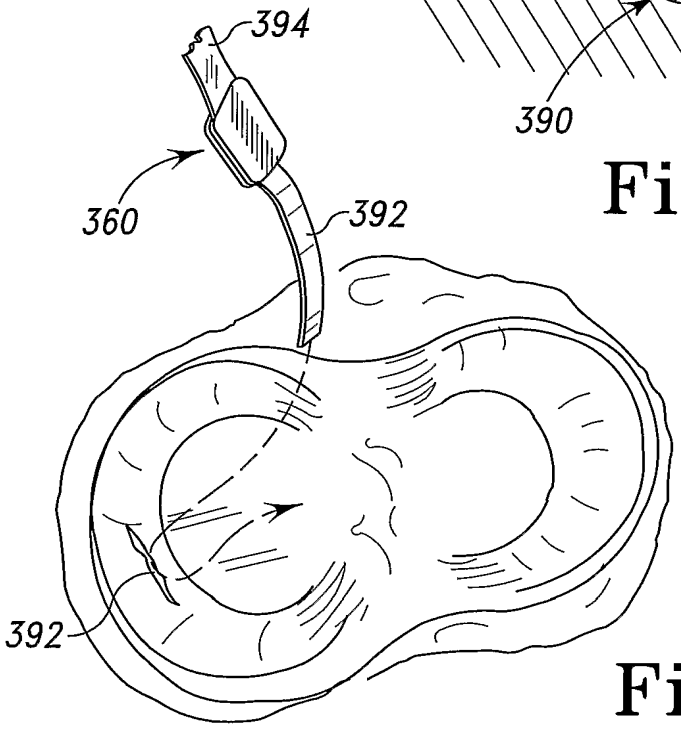

Fig. 44

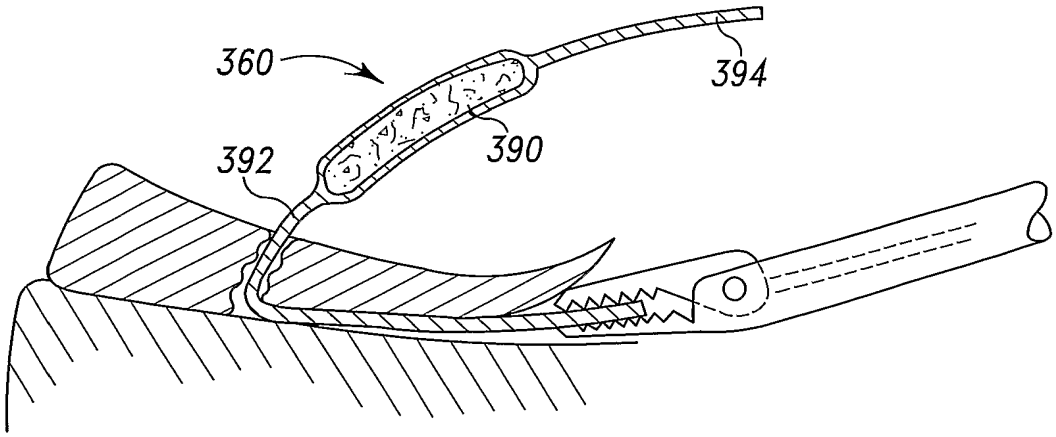

Fig. 44A

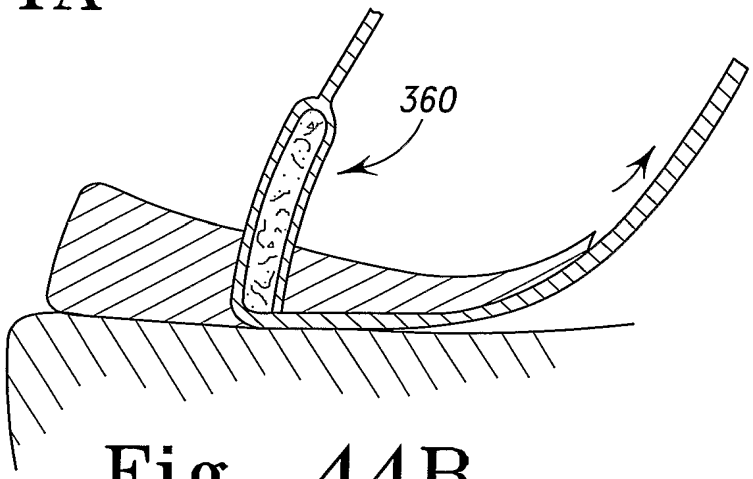

Fig. 44B

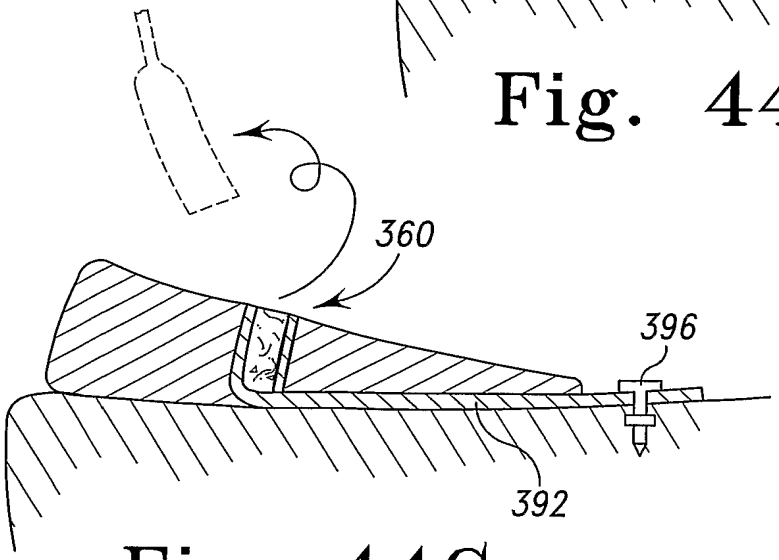

Fig. 44C

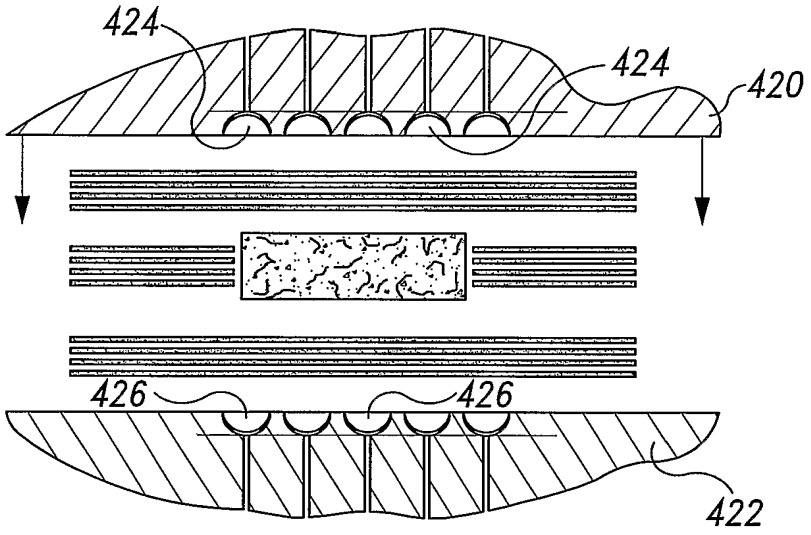

Fig. 45

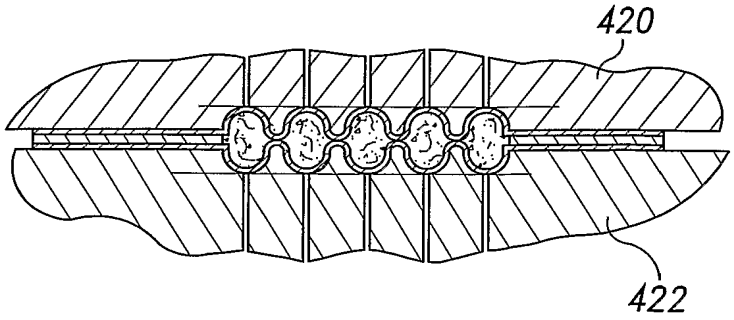

Fig. 46

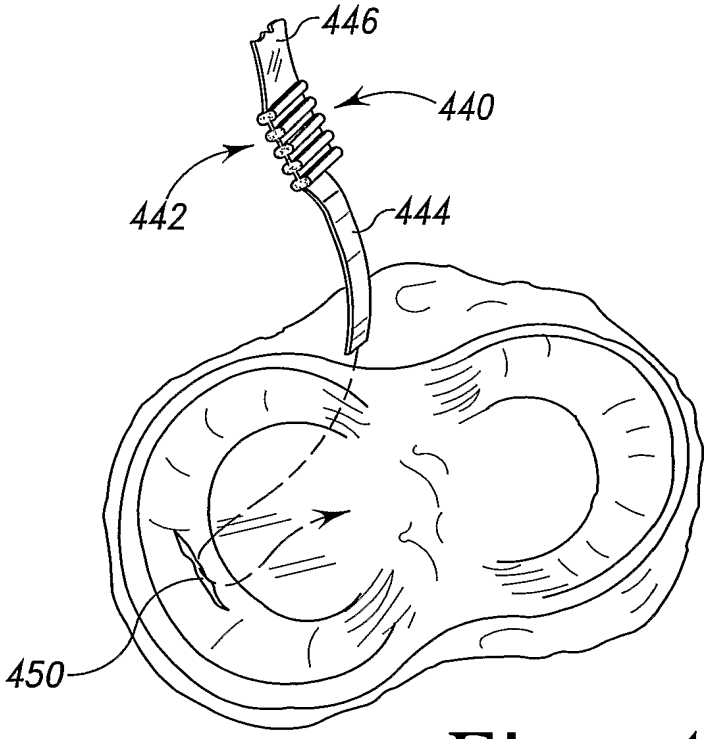

Fig. 47

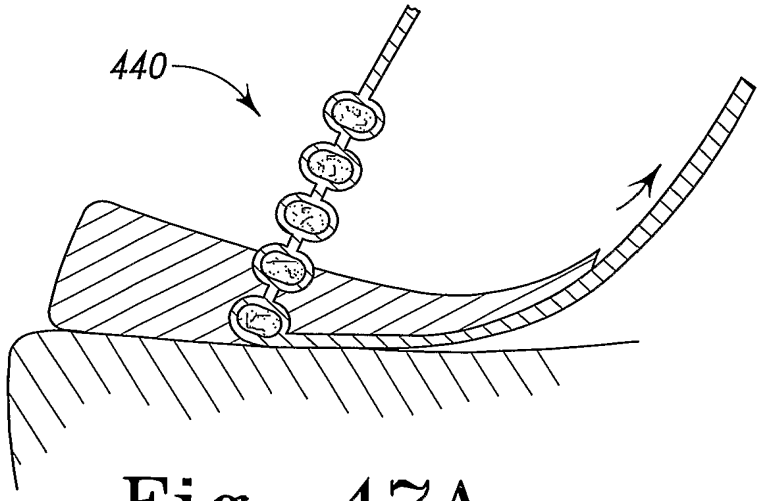

Fig. 47A

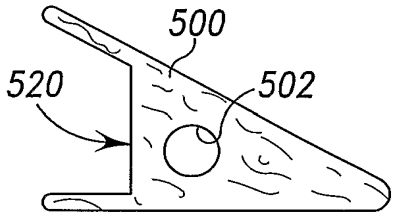

Fig. 48

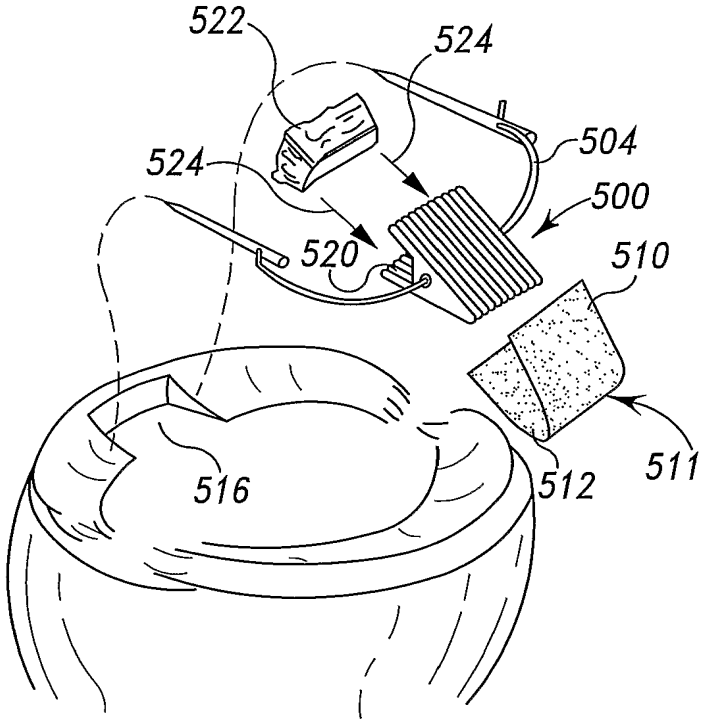

Fig. 49

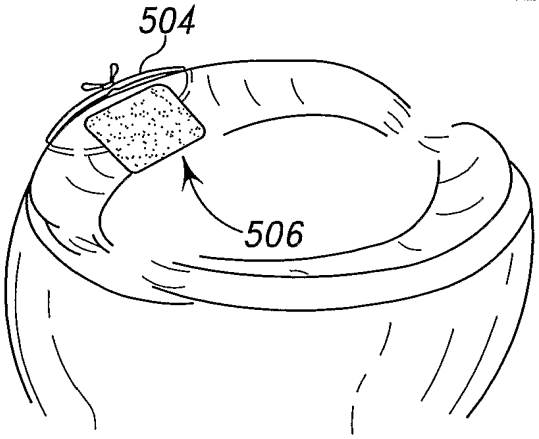

Fig. 50

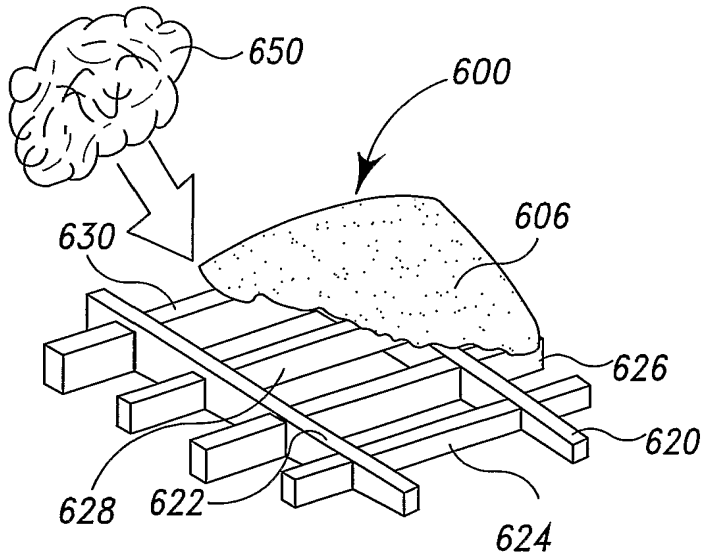

Fig. 51

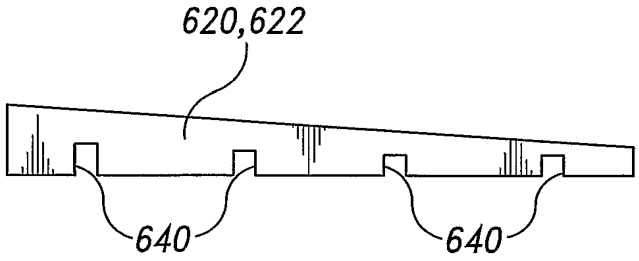

Fig. 52

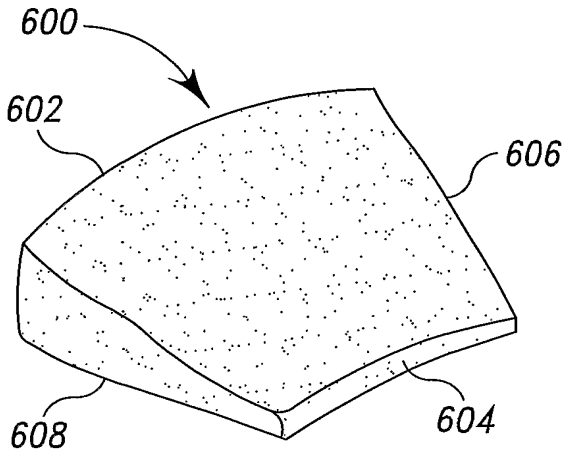

Fig. 53

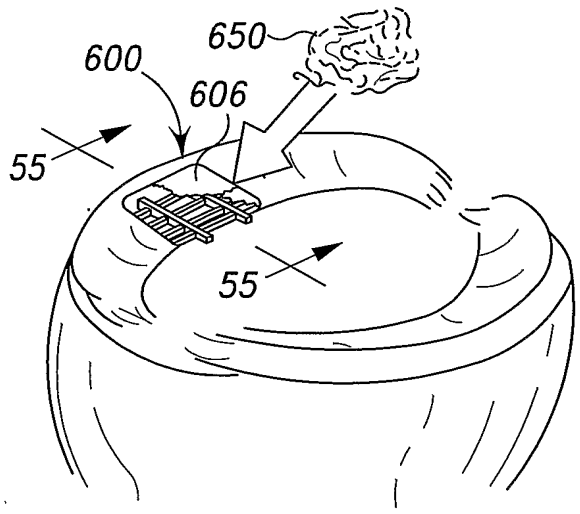

Fig. 54

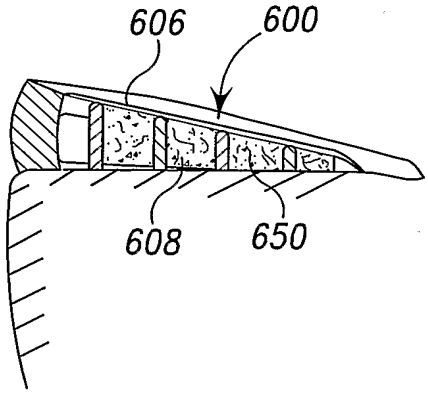

Fig. 55

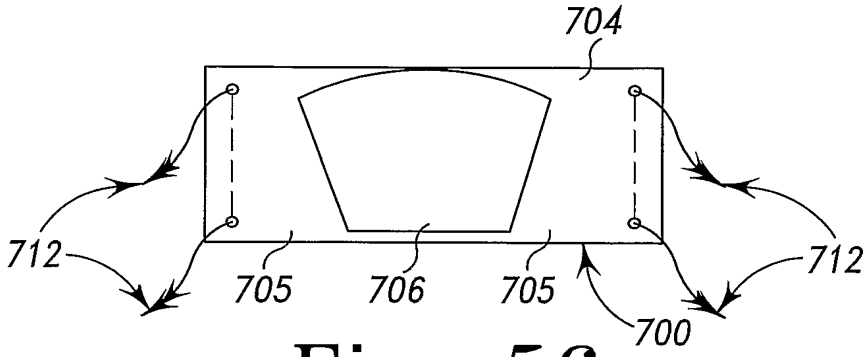

Fig. 56

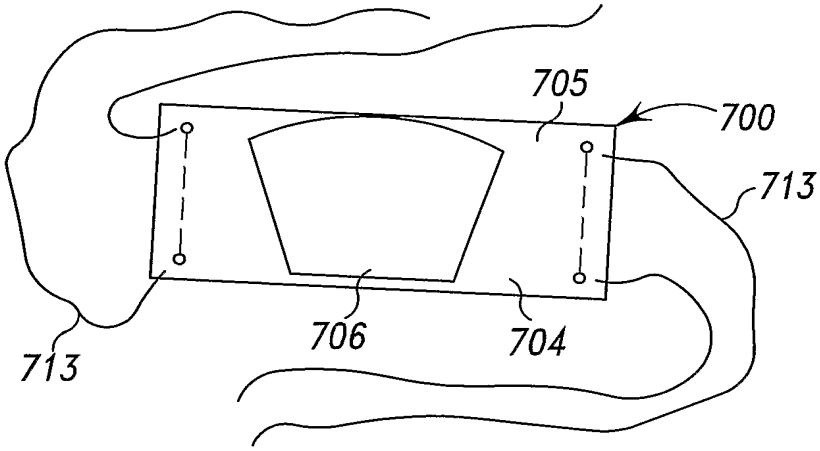

Fig. 57

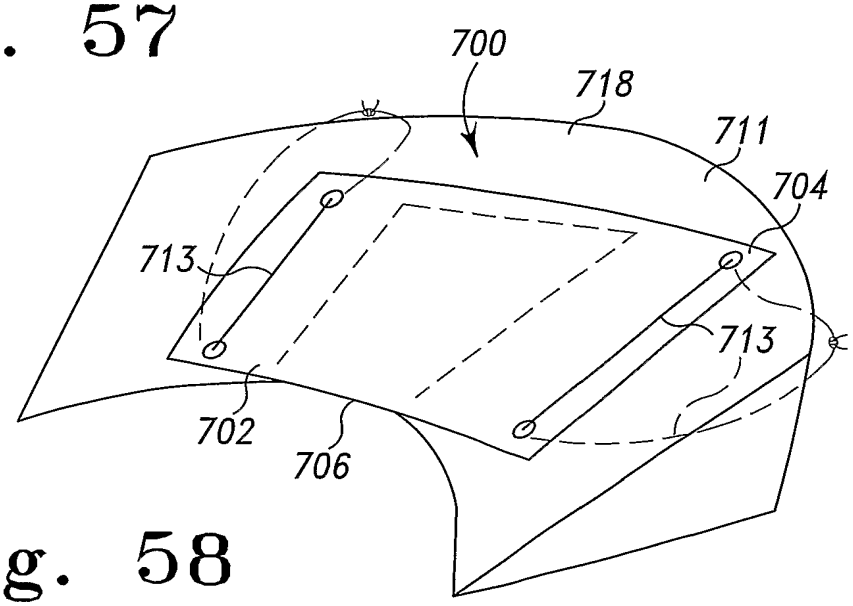

Fig. 58

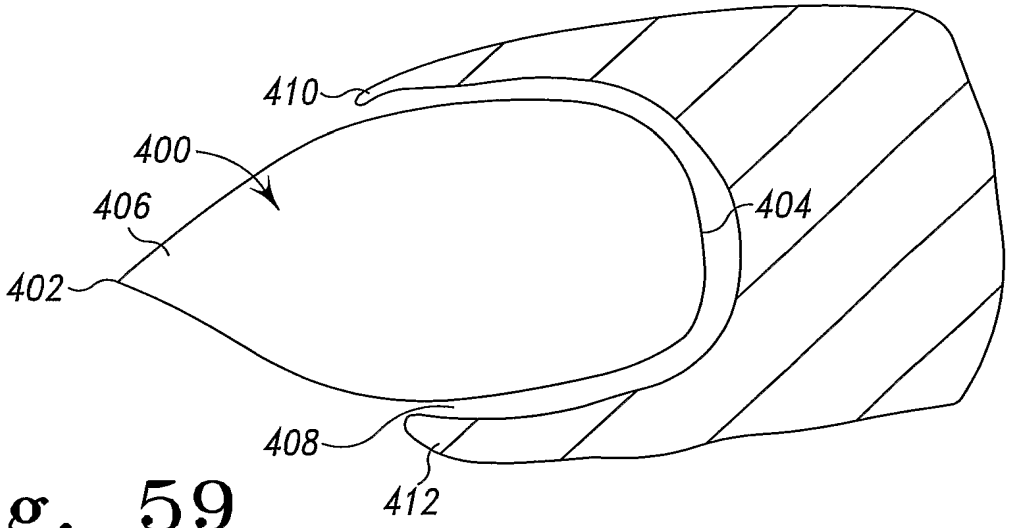

Fig. 59

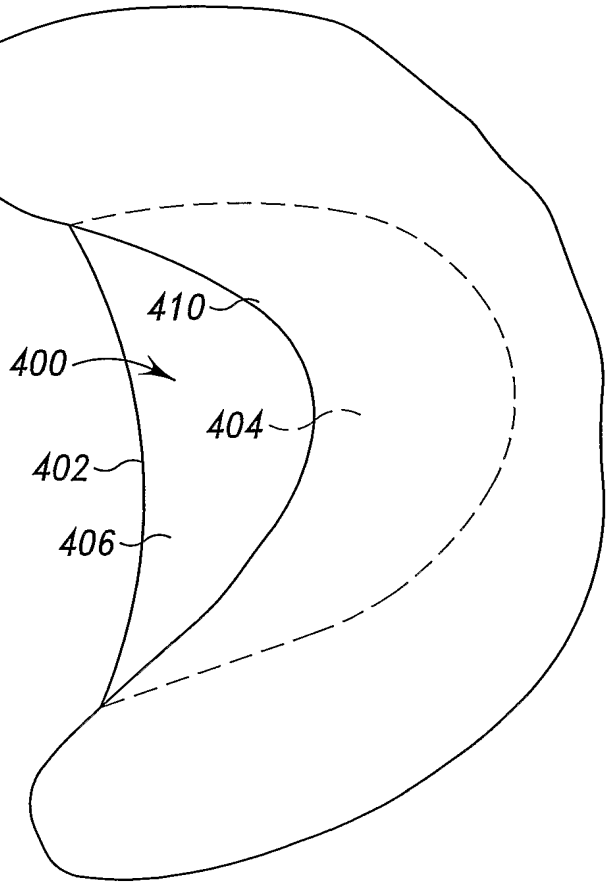

Fig. 60

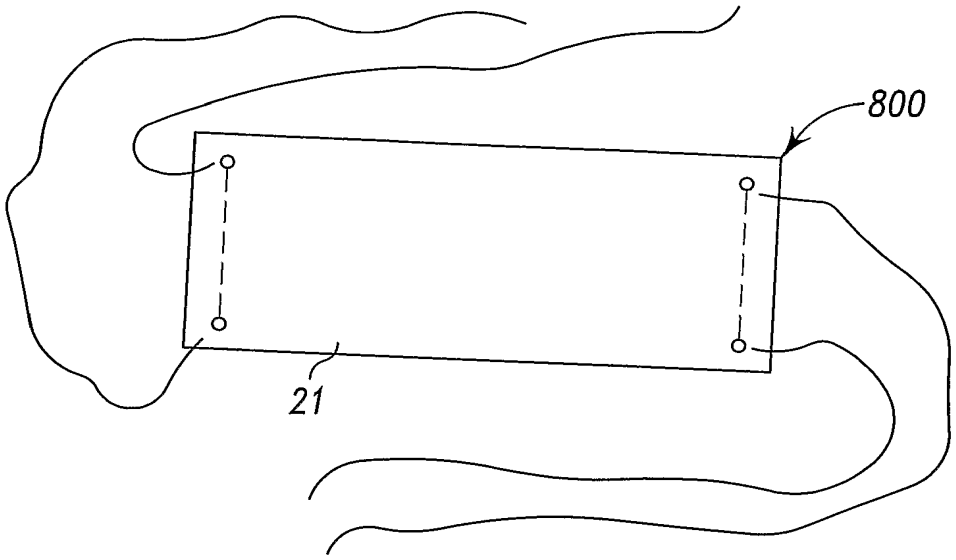

Fig. 61

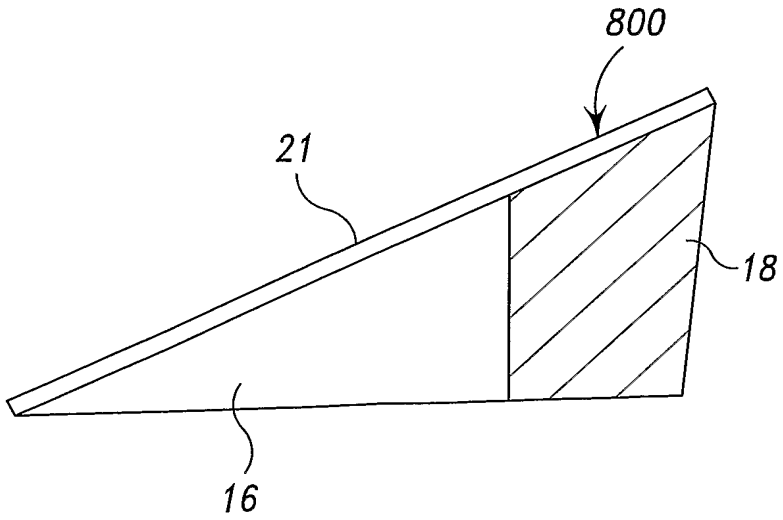

Fig. 62

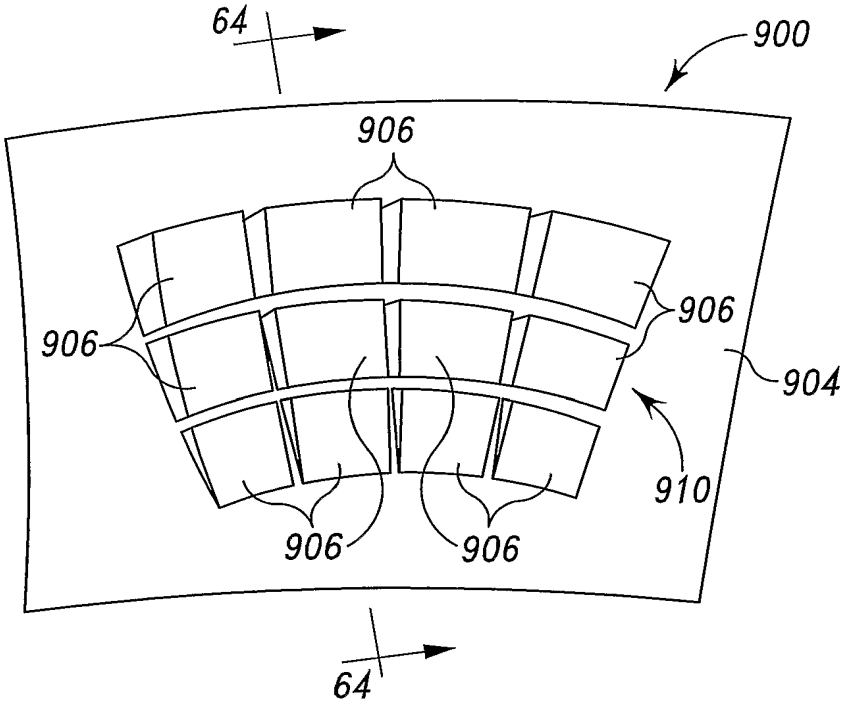

Fig. 63

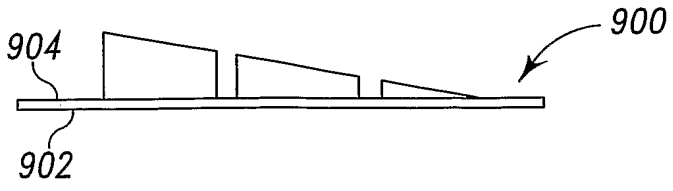

Fig. 64